



# Effect of fluticasone/salmeterol combination on dyspnea and respiratory mechanics in mild-to-moderate COPD

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Received 9 May 2012; accepted 13 January 2013

Available online 17 February 2013

## KEYWORDS

Cycle endurance;  
Chronic obstructive  
pulmonary disease;  
Exercise;  
Respiratory  
physiology;  
Work of breathing

## Summary

The purpose of this exploratory physiological study was to evaluate the effects of inhaled fluticasone/salmeterol combination (FSC) on sensory and physiological responses to exercise in subjects with mild-to-moderate COPD. In a randomized, double-blind, placebo-controlled, crossover study, subjects underwent 6-week treatments with FSC or placebo (PLA). Detailed pulmonary function and constant-work rate cycle exercise tests were performed following each treatment period. Fifteen subjects completed the study (mean  $\pm$  SD): age  $64 \pm 10$  years; smoking history  $47 \pm 29$  pack-years; post-bronchodilator forced expiratory volume in 1 s  $86 \pm 15\%$  predicted (10 mild and 5 moderate COPD); peak incremental oxygen uptake  $71 \pm 16\%$  predicted. Compared with PLA, FSC treatment was associated with improved: FEV<sub>1</sub> by  $0.23 \pm 0.18$  L; inspiratory capacity by  $0.18 \pm 0.23$  L; functional residual capacity by  $-0.28 \pm 0.30$  L; and specific airways resistance by  $-4.6 \pm 4.5$  cmH<sub>2</sub>O s (all  $p < 0.01$ ). There were no significant changes in dyspnea intensity throughout exercise and endurance time did not change significantly ( $1.2 \pm 3.0$  min,  $p = 0.149$ ). Following FSC, inspiratory capacity at rest and throughout exercise increased by  $0.2$ – $0.3$  L with concomitant increases in tidal volume and ventilation ( $p < 0.05$ ). Compared with PLA, the work of breathing and the ratio of respiratory muscle effort to tidal volume improved with FSC during exercise ( $p < 0.05$ ). In mild-to-moderate COPD, FSC was associated with significant improvements in airway function at rest and during exercise. Despite important mechanical improvements, there were no significant effects on dyspnea intensity and exercise endurance.

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## Introduction

Increased peripheral airways resistance is the hallmark of chronic obstructive pulmonary disease (COPD) and is known to be present even in patients with relatively preserved spirometry. Studies have shown active airway inflammation, loss or narrowing of peripheral airways (2–2.5 mm)<sup>1,2</sup> and increased ventilation-to-perfusion mismatching in patients with mild COPD.<sup>3,4</sup> Such patients may also exhibit evidence of increased airway wall thickness and structural emphysema.<sup>5–7</sup> Well-established manifestations of small airway dysfunction in mild COPD include: premature airway closure, mal-distribution of ventilation and increased air-trapping.<sup>3,8,9</sup> Recent cross-sectional studies confirm the vast physiological heterogeneity in mild COPD. For example, many individuals with mild COPD have clinically significant increases in airways resistance and static lung volumes as well as decreases in diffusing capacity for carbon monoxide, in highly variable combinations.<sup>9</sup>

Collectively, these diverse physiological abnormalities likely explain, at least in part, why many patients with mild COPD show increased activity-related dyspnea, reduced daily physical activity levels and decreased health-related quality of life, compared with non-smoking healthy individuals.<sup>10–13</sup> Indeed, when challenged with exercise, patients with mild COPD demonstrate higher ventilatory requirements, greater respiratory mechanical constraints, greater dyspnea intensity and exercise intolerance compared with healthy controls.<sup>12,14</sup> The main focus of this study was to better understand the respiratory mechanical derangements that exist in mild-to-moderate COPD and to determine if they can be favorably manipulated by pharmacotherapy.

Beyond the imperative of smoking cessation, there are no evidenced-based guidelines to support the routine use of pharmacotherapy in milder COPD. Nevertheless, it seems reasonable to consider pharmacotherapy in selected individuals with troublesome dyspnea and activity restriction. Such patients are rarely included in clinical trials and it remains uncertain if traditional efficacy measures (e.g., an arbitrary increase in FEV<sub>1</sub>) are relevant in this sub-population or whether other measures such as lung hyperinflation are more sensitive. A recent physiological study showed that acute administration of nebulised ipratropium bromide was associated with modest but consistent improvements in airway function and operating lung volumes during exercise.<sup>15</sup> Inhaled corticosteroids (ICS) are not recommended for mild COPD; however, there is some evidence that ICS monotherapy can improve airway hyper-responsiveness and chronic dyspnea in mild COPD.<sup>16</sup>

Studies suggest that when ICS and long-acting  $\beta_2$  agonists (LABA) are delivered as fixed combination in a single inhaler, their effect on respiratory symptoms and airway function is superior to the LABA component alone.<sup>17–19</sup> Worth et al.<sup>20</sup> recently demonstrated that treatment with combined budesonide/formoterol therapy was associated with greater cycle endurance time (by 69 s) compared with formoterol alone in patients with moderate-to-severe COPD. These trends are consistent with another study that conducted a secondary analysis on the effects of fluticasone/salmeterol combination and salmeterol alone on

pulmonary function and exercise performance in a similar population.<sup>21</sup> Fluticasone (500  $\mu$ g b.i.d.) added to foundational long-acting bronchodilator treatment has also been shown to significantly improve exercise endurance compared with placebo.<sup>22</sup> Collectively, these studies suggest that when ICS is added to LABA, bronchodilation and lung deflation are amplified and exercise tolerance is improved. The mechanisms for this amplification are disputed but non-genomic local vasoconstriction effects have been suggested.<sup>23</sup> To our knowledge, there are no studies that have examined the physiological and sensory consequences of combination therapy in mild-to-moderate COPD. Accordingly, in order to better understand the physiological abnormalities and the impact of pharmacotherapy in milder COPD, we conducted a detailed physiological study to determine the effect of inhaled fluticasone 250  $\mu$ g/salmeterol 50  $\mu$ g combination (FSC) taken twice daily in a placebo-controlled crossover study. Specifically, we evaluated the effects of 6 weeks treatment with FSC on detailed respiratory mechanics, dyspnea intensity and exercise endurance in a group of subjects with mild-to-moderate COPD and reduced exercise tolerance.

## Methods

Subjects included clinically stable subjects  $\geq 40$  years with mild-to-moderate COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (i.e., post-bronchodilator FEV<sub>1</sub> to forced vital capacity ratio (FEV<sub>1</sub>/FVC)  $< 0.7$  and FEV<sub>1</sub>  $> 60\%$  predicted)<sup>24</sup> and a cigarette smoking history  $\geq 20$  pack-years. Subjects were excluded if they had asthma or any disease other than COPD that could contribute to exercise limitation or dyspnea or the presence of any contraindication to clinical exercise testing.

## Study design

This exploratory pilot study used a randomized, double-blind, placebo-controlled, crossover design (ClinicalTrials.gov ID#: NCT00559312) and it received ethical approval from the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board (ID#: DMED-1065-07). All subjects provided informed written consent prior to participating. Two initial screening visits were designed to establish study eligibility and characterize the study population: Visit 1a included medical history, clinical assessment, dyspnea evaluation, pulmonary function tests, and a symptom-limited incremental cycle exercise test; Visit 1b included testing of pulmonary function responsiveness to 400  $\mu$ g salbutamol. At Visit 2, subjects performed pulmonary function tests and a constant-work rate (CWR) cycle exercise test for familiarization purposes. Two 6-week treatment periods with either fluticasone 250  $\mu$ g/salmeterol 50  $\mu$ g combination taken by Diskus<sup>®</sup> inhaler twice daily or a matched placebo added to the daily drug regimen were completed in randomized order with a two-week washout period between. Pulmonary function tests and a CWR cycle exercise test with detailed assessment of respiratory mechanics were performed pre-treatment (Visits 3 and 5) and post-treatment (Visits 4 and 6). Pre-

treatment measurements were collected prior to the first dose of study medication while post-treatment measurements were conducted 120 min after dosing with study medication.

Subjects were required to refrain from using ICSs and long-acting muscarinic antagonists (LAMA) for at least two weeks and LABAs for at least 48 h prior to and throughout the study. Regularly taken short-acting anticholinergics were permitted if stabilized for at least 6 weeks prior to and throughout the study. Salbutamol was permitted as rescue medication during the study. All visits were conducted in the morning. Before each visit, short-acting  $\beta_2$  agonists and anticholinergics were withheld for at least 4 and 12 h, respectively. Subjects were also required to avoid caffeine, heavy meals, alcohol, and strenuous exercise prior to visits.

## Outcome measures

The exploratory endpoints of this study were dyspnea intensity measured at a standardized time during CWR exercise, cycle endurance time, measurements of small airway function, detailed measurements of ventilation ( $V_E$ ), breathing pattern, operating lung volumes, and esophageal pressure ( $P_{es}$ )-derived indices of respiratory mechanics at rest and during exercise. Changes in chronic activity-related dyspnea were assessed post-treatment using the Transition Dyspnea Index.<sup>25</sup>

## Procedures

Spirometry, body plethysmography, single-breath diffusing capacity for carbon monoxide, maximal mouth pressures, and impulse oscillometry were performed using an automated testing system (Vs62j Body Plethysmograph, Vmax229d Encore and Masterscreen IOS; SensorMedics, Yorba Linda, CA) according to recommended guidelines.<sup>26–30</sup> The single-breath nitrogen test was used to assess the alveolar plateau ( $N_2$  slope) and closing volume.<sup>8,31</sup> Static lung compliance ( $C_{Lst}$ ) and lung recoil pressure ( $P_{Lst}$ ) were also measured (Vs62j; SensorMedics). Pulmonary function measurements were expressed as percentages of predicted normal values.<sup>32–36</sup>

Symptom-limited exercise tests were conducted on an electronically braked cycle ergometer (Ergometrics 800S; SensorMedics) using a cardiopulmonary exercise testing system (Vmax229d; SensorMedics). The incremental cycle test consisted of stepwise increases in work rate of 10 W/min with peak work rate ( $W_{peak}$ ) defined as the greatest work rate the subject could sustain for at least 30 s. CWR cycle tests on subsequent visits were performed at 85%  $W_{peak}$  with endurance time defined as the duration of loaded pedaling. Cardiopulmonary parameters, breathing pattern and  $P_{es}$ -derived measurements of respiratory mechanics were assessed on a breath-by-breath basis. Operating lung volumes were derived from inspiratory capacity (IC) measurements performed at rest, every second minute during exercise and at end-exercise. Heart rate, oxyhemoglobin saturation and blood pressure were measured using electrocardiography, pulse oximetry and sphygmomanometry, respectively. Subjects rated the intensity of their “breathing discomfort” and “leg discomfort” at rest, every minute

during exercise and at end-exercise using the modified 10-point Borg scale.<sup>37</sup> At exercise cessation, subjects were asked about their main reason for stopping exercise and selected various qualitative descriptors of their breathing.<sup>38</sup>  $P_{es}$  was measured continuously during post-treatment exercise tests using a balloon-tipped catheter (Ackrad Laboratories, Cranford, NJ) and an integrated data acquisition system. The mechanical work of breathing ( $W_b$ ) was calculated as the area within the tidal  $P_{es}$ -volume loop and the additional work that fell outside of the loop representing part of the elastic  $W_b$ . An index of neuromechanical coupling was calculated as the ratio of tidal  $P_{es}/P_{I_{max}}$  to tidal volume (VT)/predicted vital capacity (VC)<sup>39</sup> where  $P_{I_{max}}$  was the maximal inspiratory  $P_{es}$  from sniff maneuvers.<sup>40</sup> Exercise test data were evaluated at rest, at standardized times during exercise and at peak exercise (the last 30-s of loaded pedaling). *Isotime* was defined as the highest test duration achieved on all testing days rounded down to the nearest full minute where an IC maneuver was performed.

## Statistical analyses

Primary statistical comparisons were performed on post-treatment measurements of FSC versus PLA. Possible crossover and period effects for all exploratory endpoints were first assessed using paired *t*-tests according to recommended guidelines.<sup>41</sup> Treatment responses were compared using paired *t*-tests. Reasons for stopping exercise and dyspnea descriptors were analyzed using McNemar's exact test. A  $p < 0.05$  significance level was used for all analyses, with Bonferroni adjustments for multiple comparisons where appropriate. Values are presented as mean  $\pm$  SD unless otherwise specified.

## Results

Eighteen subjects were enrolled prior to termination of the study due to expiry of study medication: 3 subjects were subsequently withdrawn (2 for personal reasons, 1 due to an acute COPD exacerbation after the first week of study treatment), 15 subjects completed the study, and 11 of the completed subjects had  $P_{es}$ -derived measurements at both post-treatment visits. All subjects had a significant smoking history and a diagnosis of COPD, the majority of whom (13/18) had a diagnosis within the previous 5 years. Post-bronchodilator  $FEV_1/FVC$  ratios were  $<0.70$  and all but two subjects were  $<$ lower limit of normal.<sup>42</sup>  $FEV_1$  %predicted fit either GOLD stage I ( $n = 12$ ) or stage II ( $n = 6$ ) criteria for COPD. Subjects had mild-to-moderate activity-related dyspnea, reduced symptom-limited cycle exercise capacity, as well as an abnormal ventilatory response during exercise (Table 1). The majority of the sample used regular respiratory medications: a short-acting  $\beta_2$  agonist as needed ( $n = 10$ ), ipratropium ( $n = 3$ ), tiotropium ( $n = 4$ ), salmeterol ( $n = 2$ ), fluticasone ( $n = 2$ ) and salmeterol/fluticasone ( $n = 3$ ).

Treatment responses are reported for the 15 completed subjects (GOLD stage I = 10; GOLD stage II = 5). There was no significant crossover or period effects for any of the exploratory endpoints. The only treatment-related adverse event was moderate-to-severe hoarseness in 4 subjects during the FSC arm. The Transition Dyspnea Index revealed

**Table 1** Subject characteristics at baseline.

	Enrolled subjects (n = 18)	Completed subjects (n = 15)	Subjects with mechanical measurements (n = 11)
Sex	39% male	40% male	45% male
Age, years	64 ± 10	64 ± 10	63 ± 10
Body mass index, kg/m <sup>2</sup>	28.3 ± 6.5	29.5 ± 6.4	31.6 ± 5.8
COPD duration, years	4.9 ± 5.7	4.5 ± 5.1	3.1 ± 2.2
Cigarette smoking, pack-years	43 ± 28	47 ± 29	47 ± 34
Baseline Dyspnea Index, focal score	8.3 ± 1.5	8.3 ± 1.6	8.5 ± 1.7
Peak incremental VO <sub>2</sub> , L/min	1.34 ± 0.44	1.39 ± 0.46	1.45 ± 0.50
(%predicted max)	(69 ± 15)	(71 ± 16)	(67 ± 13)
Peak incremental work rate,	79 ± 29	79 ± 32	86 ± 33
W (%predicted max)	(59 ± 14)	(59 ± 15)	(58 ± 14)
Peak incremental ΔIC, L	0.38 ± 0.29	0.39 ± 0.30	0.43 ± 0.31
<b>Pulmonary function:</b>			
<i>post-bronchodilator:</i>			
FEV <sub>1</sub> , %predicted	87 ± 14	86 ± 15	87 ± 15
FEV <sub>1</sub> /FVC, %	60 ± 6	61 ± 6	60 ± 5
<i>pre-bronchodilator:</i>			
FEV <sub>1</sub> , %predicted	80 ± 17	79 ± 19	79 ± 17
FEV <sub>1</sub> /FVC, %	58 ± 9	58 ± 9	57 ± 8
SVC, %predicted	104 ± 19	101 ± 17	104 ± 17
IC, %predicted	100 ± 23	99 ± 24	105 ± 16
FRC, %predicted	105 ± 16	102 ± 16	100 ± 13
RV, %predicted	107 ± 23	106 ± 24	107 ± 24
TLC, %predicted	103 ± 12	101 ± 11	102 ± 11
D <sub>LCO</sub> , %predicted	68 ± 20	68 ± 20	64 ± 19
MIP, %predicted	103 ± 28	100 ± 27	103 ± 27
MEP, %predicted	71 ± 18	69 ± 19	72 ± 16
N <sub>2</sub> slope, %predicted	628 ± 676	644 ± 724	652 ± 811

Values are means ± SD.

Abbreviations: VO<sub>2</sub>, oxygen uptake; ΔIC, change in inspiratory capacity from rest (i.e., magnitude of dynamic hyperinflation); FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; SVC, slow vital capacity; IC, inspiratory capacity; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; D<sub>LCO</sub>, lung diffusing capacity for carbon monoxide; MIP, maximal inspiratory mouth occlusion pressure at functional residual capacity; MEP, maximal expiratory mouth occlusion pressure at total lung capacity.

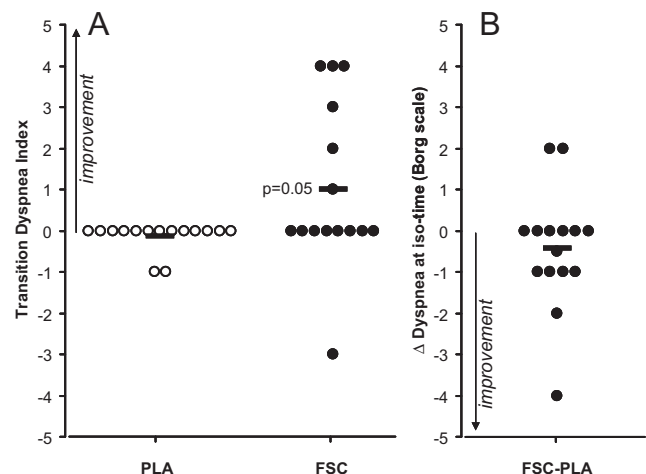
modest but non-significant improvements in activity-related dyspnea after treatment with FSC compared with PLA (1.00 ± 2.00 vs. 0.13 ± 0.35 units, respectively; *p* = 0.05) (Fig. 1A).

## Pulmonary function

Post-treatment pulmonary function data are shown in Table 2. Six weeks of FSC therapy was associated with significant improvements in pre- (*trough*) and post-dose (*peak*) FEV<sub>1</sub>, functional residual capacity, inspiratory capacity and specific airways resistance. Impulse oscillometry measurements that changed significantly included post-dose values of total resistance at 5 Hz (R5), reactance at 5 Hz (X5) and resonant frequency (Fres); while measurements at the higher frequencies (i.e., 15 and 20 Hz) did not change. There were no significant treatment differences in closing volume or N<sub>2</sub> slope.

## Exercise responses

On average, dyspnea intensity during exercise was not significantly different following FSC compared with PLA at



**Figure 1** Responders and non-responders for the change in dyspnea at isotime and the Transition Dyspnea Index during constant-work rate exercise. FSC, fluticasone/salmeterol combination; PLA, placebo.

**Table 2** Post-treatment pulmonary function ( $n = 15$ ).

	PLA		FSC	
	Trough	Peak	Trough	Peak
FEV <sub>1</sub> , L	1.78 ± 0.77	1.81 ± 0.74	1.94 ± 0.77 *	2.04 ± 0.80 *
FEV <sub>1</sub> /FVC, %	57 ± 7	57 ± 8	60 ± 6 *	60 ± 6 *
PEF, L/s	5.19 ± 1.80	5.23 ± 1.73	5.62 ± 1.78	5.72 ± 1.80 *
FEF <sub>25–75%</sub> , L/s	0.77 ± 0.50	0.79 ± 0.50	0.87 ± 0.62	0.91 ± 0.58 *
SVC, L	3.30 ± 1.18	3.36 ± 1.17	3.38 ± 1.04	3.50 ± 1.16 *
IC, L	2.53 ± 1.02	2.59 ± 1.10	2.68 ± 1.13 *	2.77 ± 1.12 *
FRC, L	3.04 ± 0.65	2.99 ± 0.67	2.89 ± 0.61 *	2.71 ± 0.54 *
RV, L	2.26 ± 0.71	2.21 ± 0.69	2.20 ± 0.68	2.04 ± 0.62
TLC, L	5.56 ± 1.41	5.57 ± 1.47	5.58 ± 1.49	5.50 ± 1.35
sRaw, cmH <sub>2</sub> O s	13.9 ± 6.1	14.3 ± 7.6	11.1 ± 5.0 *	9.6 ± 3.6 *
D <sub>LCO</sub> , mL/min/mmHg	13.6 ± 5.5	13.4 ± 5.5	14.4 ± 6.0	14.2 ± 5.8
MIP, cmH <sub>2</sub> O	72 ± 23	76 ± 22	75 ± 21	81 ± 21
R5, cmH <sub>2</sub> O/L/s	6.9 ± 2.2	6.9 ± 2.1	6.6 ± 2.2	6.1 ± 1.8 *
X5, cmH <sub>2</sub> O/L/s	−2.8 ± 1.7	−3.2 ± 2.0	−2.2 ± 1.0	−2.0 ± 1.0 *
Fres, Hz	21.4 ± 5.6	21.9 ± 5.7	19.0 ± 5.3	16.8 ± 5.3 *
Closing volume, L	—	0.46 ± 0.32	—	0.54 ± 0.44
N <sub>2</sub> slope, %/L	—	6.4 ± 4.3	—	5.8 ± 3.3
C <sub>Lst</sub> , L/cmH <sub>2</sub> O #	—	0.31 ± 0.10	—	0.35 ± 0.15
P <sub>Lst</sub> , cmH <sub>2</sub> O #	—	25.5 ± 11.9	—	22.6 ± 8.0

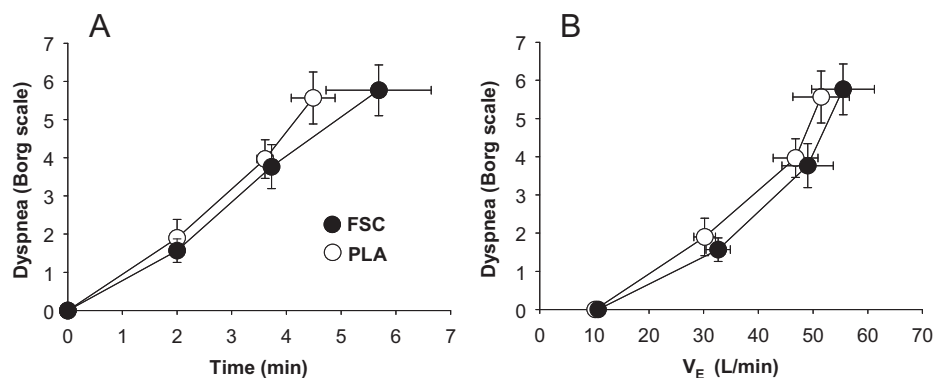
Values are means ± SD. \*  $p < 0.05$  FSC versus PLA; #  $n = 11$ .

Abbreviations: FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; FEF<sub>25–75%</sub>, forced expiratory flow between 25 and 75% of forced vital capacity; SVC, slow vital capacity; IC, inspiratory capacity; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; sRaw, specific airways resistance; D<sub>LCO</sub>, lung diffusing capacity for carbon monoxide; MIP, maximal inspiratory mouth occlusion pressure at functional residual capacity; R5, resistance at 5 Hz; X5, reactance at 5 Hz; Fres, resonant frequency; C<sub>Lst</sub>, static lung compliance; P<sub>Lst</sub>, static lung elastic recoil pressure.

any given time or  $V_E$  (Fig. 2). However, 6/15 subjects experienced a  $\geq 1$  Borg unit decrease and 7/15 a  $\geq 0.5$  Borg unit decrease in dyspnea intensity at isotime following treatment (Fig. 1B). Primary reasons for stopping exercise following PLA [breathing ( $n = 4$ ), legs ( $n = 5$ ), combination of legs and breathing ( $n = 5$ ), other ( $n = 1$ )] were not significantly different from FSC [breathing ( $n = 1$ ), legs ( $n = 8$ ), combination ( $n = 5$ ), other ( $n = 1$ )].

Exercise responses are reported in Table 3. Although there was a  $1.2 \pm 3.0$  min mean difference in favor of FSC in post-treatment CWR cycle endurance time, this did not reach statistical significance ( $p = 0.149$ ). FSC had no effect

on oxygen uptake ( $\dot{V}O_2$ ) or heart rate at rest and throughout exercise. Ventilatory responses to exercise are shown in Fig. 3.  $V_E$  increased during exercise with FSC as a result of an increase in  $V_T$ . IC at isotime was increased by 0.23 L, reflecting the increase in IC at rest by 0.22 L; this resulted in a downward shift in operating lung volumes at rest and throughout exercise (Fig. 3E). During the latter stages of exercise (~4 min) after FSC compared with PLA, the total mechanical  $W_b$  was significantly reduced by 16 J/min (15%) and  $P_{es}$  swings decreased by 6 cmH<sub>2</sub>O (20%) despite the increase in  $V_E$  (Fig. 3). The ratio of respiratory effort to  $V_T$ , a crude measure of neuromechanical coupling of the



**Figure 2** Dyspnea versus time and ventilation ( $V_E$ ) during constant-work rate exercise. FSC, fluticasone/salmeterol combination; PLA, placebo. Values are means ± SE.



**Table 3** Sensory and physiological responses at rest, isotime and peak exercise ( $n = 15$ ).

	Rest		Isotime		Peak	
	PLA	FSC	PLA	FSC	PLA	FSC
Exercise time, min	—	—	3.3 ± 1.4	3.3 ± 1.4	4.5 ± 1.6	5.7 ± 3.7
Dyspnea, Borg	0.0 ± 0.0	0.0 ± 0.0	3.2 ± 2.4	2.8 ± 1.9	5.6 ± 2.6	5.8 ± 2.6
Leg discomfort, Borg	0.0 ± 0.0	0.0 ± 0.0	4.1 ± 2.4	3.8 ± 2.2	6.4 ± 2.8	6.4 ± 2.5
VO <sub>2</sub> , L/min	0.30 ± 0.10	0.29 ± 0.09	1.27 ± 0.47	1.28 ± 0.51	1.41 ± 0.48	1.45 ± 0.56
Heart rate, beats/min	79 ± 13	83 ± 13	116 ± 19	118 ± 18	126 ± 21	128 ± 17
SaO <sub>2</sub> , %	96 ± 4	96 ± 3	94 ± 6	96 ± 4	96 ± 6	96 ± 4
V <sub>E</sub> , L/min	10.2 ± 2.6	10.7 ± 2.7	40.4 ± 18.1	43.8 ± 20.5 *	51.5 ± 20.0	55.5 ± 22.2 *
V <sub>T</sub> , L	0.69 ± 0.20	0.69 ± 0.15	1.44 ± 0.48	1.55 ± 0.61 *	1.48 ± 0.49	1.63 ± 0.64 *
F <sub>b</sub> , breaths/min	15.6 ± 4.7	16.3 ± 5.3	27.9 ± 6.4	28.8 ± 7.8	35.3 ± 8.0	35.2 ± 8.7
T <sub>I</sub> /T <sub>tot</sub>	0.40 ± 0.05	0.43 ± 0.07 *	0.43 ± 0.05	0.44 ± 0.04	0.44 ± 0.05	0.45 ± 0.05
V <sub>E</sub> /VCO <sub>2</sub>	42 ± 8	44 ± 9	31 ± 4	33 ± 4 *	33 ± 5	34 ± 4 *
P <sub>ET</sub> CO <sub>2</sub> , mmHg	34 ± 3	34 ± 4	37 ± 5	36 ± 4 *	35 ± 6	34 ± 5 *
IC, L	2.52 ± 0.96	2.74 ± 1.12 *	2.30 ± 1.00	2.53 ± 1.11 *	2.24 ± 1.03	2.41 ± 1.03 *
ΔIC, L	0.0 ± 0.0	0.0 ± 0.0	-0.22 ± 0.25	-0.21 ± 0.26	-0.28 ± 0.29	-0.33 ± 0.28
IRV, L	1.83 ± 0.85	2.06 ± 1.06 *	0.86 ± 0.67	0.98 ± 0.71	0.76 ± 0.63	0.78 ± 0.47
P <sub>es</sub> tidal swing, cmH <sub>2</sub> O #	10 ± 3	9 ± 3	28 ± 11	23 ± 7 *	35 ± 18	31 ± 16 *
W <sub>b</sub> , J/min #	6 ± 3	5 ± 3	82 ± 47	76 ± 45	138 ± 80	135 ± 79
P <sub>es</sub> /P <sub>I</sub> <sub>max</sub> :V <sub>T</sub> /VC <sub>pred</sub> #	0.69 ± 0.30	0.52 ± 0.12	0.87 ± 0.44	0.61 ± 0.22 *	1.07 ± 0.62	0.78 ± 0.43 *

Values are means ± SD. \*  $p < 0.05$  FSC versus PLA; #  $n = 11$ .

Abbreviations: VO<sub>2</sub>, oxygen uptake; SaO<sub>2</sub>, arterial oxygen saturation; V<sub>E</sub>, minute ventilation; V<sub>T</sub>, tidal volume; F<sub>b</sub>, breathing frequency; T<sub>I</sub>/T<sub>tot</sub>, inspiratory duty cycle; V<sub>E</sub>/VCO<sub>2</sub>, ventilatory equivalent for carbon dioxide; P<sub>ET</sub>CO<sub>2</sub>, partial pressure of end-tidal carbon dioxide; IC, inspiratory capacity; ΔIC, change in inspiratory capacity from rest; IRV, inspiratory reserve volume; P<sub>es</sub>, esophageal pressure; W<sub>b</sub>, work of breathing; P<sub>I</sub><sub>max</sub>, maximal inspiratory pressure from a sniff maneuver; VC<sub>pred</sub>, predicted vital capacity; P<sub>es</sub>/P<sub>I</sub><sub>max</sub>:V<sub>T</sub>/VC<sub>pred</sub>, index of neuromechanical coupling.

respiratory system, improved at isotime and peak exercise following treatment with FSC by 35% and 31%, respectively (Table 3).

## Discussion

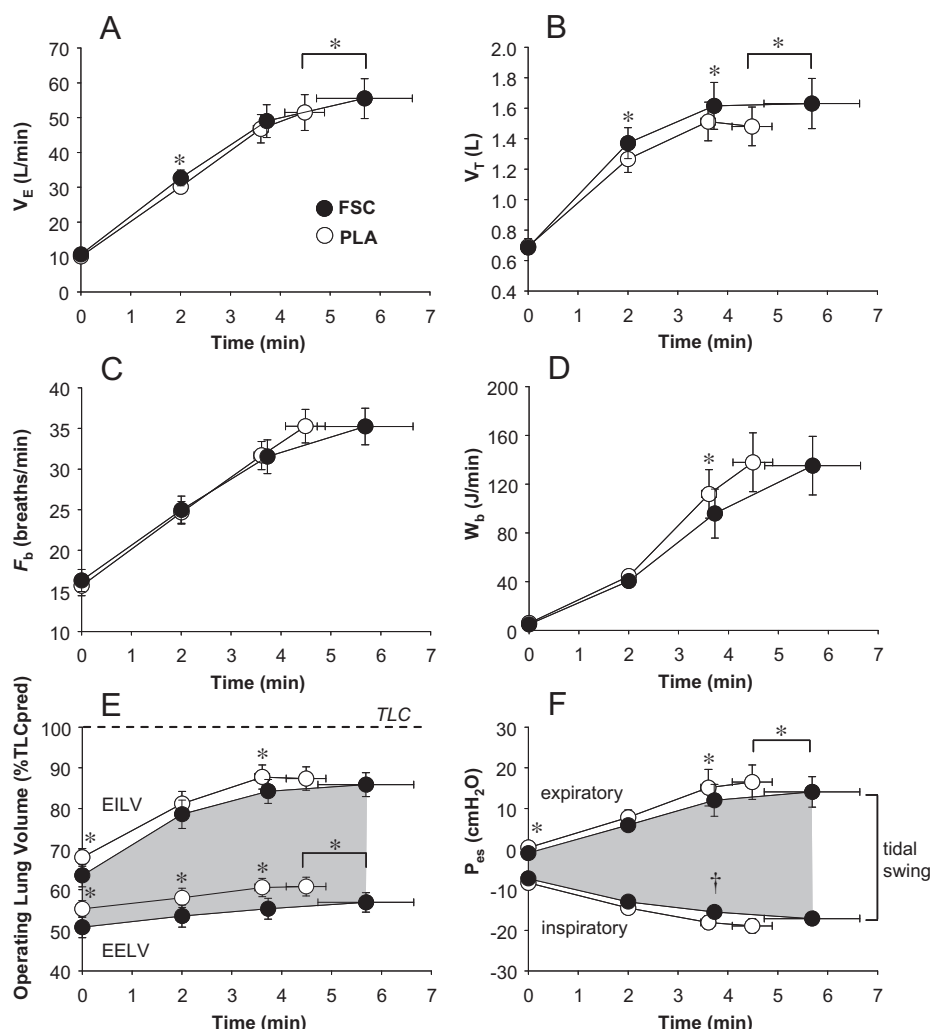
The main findings of this exploratory physiological study are as follows: (1) compared with PLA, FSC did not significantly improve dyspnea intensity ratings during high intensity CWR exercise or the Transition Dyspnea Index; (2) FSC was associated with significant improvements in trough and peak FEV<sub>1</sub> and airways resistance with concomitant improvements in FRC; (3) FSC significantly increased IC during rest and exercise and reduced respiratory muscle effort requirements and the mechanical W<sub>b</sub>.

Our subjects with mild-to-moderate COPD had clear evidence of physiological impairment and experienced mild-to-moderate dyspnea during daily activity as measured by the Baseline Dyspnea Index. Our results therefore add to the growing body of evidence that some patients with mild spirometric abnormalities experience persistent troublesome dyspnea and activity restriction.<sup>12,13</sup> Approximately 70% of the study participants were already receiving regular inhaled pharmacotherapy for their symptoms. Despite having a relatively preserved FEV<sub>1</sub>, our subjects showed evidence of extensive peripheral airway dysfunction which included: markedly reduced maximal mid-expiratory flows, increased resistance at low oscillation frequencies and mal-distribution of ventilation as measured by single-breath N<sub>2</sub> washout. These subjects also had

significantly reduced exercise tolerance: peak cycle work rate was only 59% predicted and peak symptom-limited VO<sub>2</sub> was only 17 ± 4 ml/kg/min (71% predicted). In agreement with previous studies in mild COPD, end-expiratory lung volume increased from rest to peak incremental exercise (by ~0.4 L) and subjects experienced strong dyspnea in intensity at relatively low absolute work rates and ventilations compared to previously studied age-matched healthy controls.<sup>12,14</sup> Respiratory mechanical measurements and ventilatory responses were similar in this group to those reported in previous studies in mild COPD.<sup>12,14,15</sup> However, despite these respiratory mechanical abnormalities, only 2/15 subjects identified dyspnea as the sole reason for stopping pre-treatment CWR exercise.

## Resting pulmonary function treatment responses

Six-week treatment with FSC was associated with significant improvements in airway function measured by spirometry, forced oscillometry and plethysmography (specific airways resistance decreased by an average of 39%). Trough FEV<sub>1</sub> increased by an average of 160 ml (9%) indicating effective sustained 12 h bronchodilation. Resting IC and VC increased significantly, and FRC decreased confirming a modest reduction in air-trapping. The magnitude of effect is comparable to that observed following acute administration of high-dose nebulized ipratropium bromide in similar subjects with mild COPD.<sup>15</sup> However, greater reduction in lung hyperinflation was previously seen when



**Figure 3** Ventilatory and respiratory mechanical responses to constant-work rate exercise.  $V_E$ , ventilation;  $V_T$ , tidal volume;  $F_b$ , breathing frequency;  $W_b$ , work of breathing; EILV, end-inspiratory lung volume; EELV, end-expiratory lung volume; TLC, total lung capacity; TLCpred, predicted total lung capacity;  $P_{es}$ , esophageal pressure; FSC, fluticasone/salmeterol combination; PLA, placebo. \*  $p < 0.05$ ; †  $p = 0.05$ . Panels D and F ( $n = 11$ ). Values are means  $\pm$  SE.

FSC was administered in subjects with more severe airway obstruction.<sup>21</sup>

### Exercise treatment responses

In keeping with previous bronchodilator studies in more advanced COPD,  $V_E$  increased at isotime and at peak exercise with FSC by 3.4 and 4.0 L/min, respectively, which was primarily attributable to corresponding small increases in  $V_T$  expansion by 0.11 and 0.15 L. Breathing frequency responses to exercise were similar with PLA and FSC. The ventilatory equivalent for  $CO_2$  increased modestly following FSC compared with PLA because of relatively greater increases in the numerator ( $V_E$ ); accordingly, there was a concomitant decrease in end-tidal  $CO_2$  throughout exercise. Both end-inspiratory and end-expiratory lung volumes were reduced primarily as a result of increased resting IC as the rate of change in IC (i.e., dynamic lung hyperinflation) was unchanged (Table 3). Lung volume reduction likely reflected improved mechanical time constants for lung

emptying mainly as a result of decreased airways resistance since  $P_{Lst}$  was not altered post-FSC. Subjects could achieve a higher  $V_E$  throughout exercise at lower operating lung volumes (Fig. 3) which is likely advantageous for respiratory muscle function. Indeed, tidal  $P_{es}$  swings and the total mechanical  $W_b$  were both reduced during exercise as a result of reduced resistive and elastic loading. Moreover, FSC treatment was associated with an improved ratio of respiratory effort to  $V_T$  (by  $>30\%$  at isotime and peak exercise) suggesting a more favorable relation between central neural drive and the mechanical response of the respiratory system during exercise.

### Dyspnea

The question arises as to why the aforementioned improvements in airway function and respiratory mechanics did not translate into improved dyspnea and exercise tolerance for the group as a whole? This inconsistency is in sharp contrast with the results of previous studies on the

effects of FSC and bronchodilator therapy in subjects with moderate-to-severe COPD.<sup>21,43</sup> A minority of subjects (6/15) did show improvement in dyspnea after FSC treatment as measured by isotime dyspnea ratings of  $\geq 1$  Borg units or Transition Dyspnea Index of  $\geq 1$  (the minimal clinically important difference). The variable dyspnea responses following treatment (Fig. 1) may have been attributable to the fact that the resting IC was largely preserved in these subjects and that in contrast to more severe COPD,<sup>44</sup> leg discomfort (or a combination of leg and breathing discomfort) was reported as an important reason for stopping CWR exercise in the majority. It is also possible that, unlike the situation in previous studies of FSC efficacy in moderate-to-severe COPD, the smaller improvements in respiratory mechanics in milder COPD were insufficient to counter the negative sensory effects of the attendant increase in  $V_E$ . In this regard, it is noteworthy that, in contrast to similar bronchodilator studies in more advanced COPD,<sup>45</sup> FSC did not alter the relationship between dyspnea intensity and  $V_E$  during exercise in milder COPD. It remains to be determined if alternative exercise modalities (e.g., treadmill), which may theoretically be associated with less perceived leg discomfort, might prove more suitable for the purpose of dyspnea evaluation in milder COPD.

## Limitations

This was an invasive and mechanistic physiological study that utilized a rigorous experimental approach in a relatively small number of patients and not a traditional clinical trial. As such, we may have been underpowered to detect significant treatment differences in variables such as isotime dyspnea and exercise performance. As such, caution must be made when extrapolating these data to the larger population of patients with mild-to-moderate COPD. Nevertheless, our sample size was sufficiently large to detect consistent changes in several physiological variables in response to FSC treatment and provided new insights into the drugs mode of action in milder disease. This study provides a strong rationale for future studies to identify symptomatic patients with mild COPD who are likely to respond to FSC treatment.

Our COPD patients had an average BMI of 29.5 kg/m<sup>2</sup>, with 7 subjects in the obese range. This may have implications for measured lung volume components in this study group<sup>46</sup> and potentially for physiological and sensory responses to FSC treatment. However, this latter contention is untested and remains speculative.

## Conclusions

Compared to PLA, no consistent improvement in dyspnea and exercise tolerance was observed in those randomized to FSC. Our results confirm that extensive physiological derangements and exercise intolerance can exist in some patients with mild COPD and that FSC treatment was associated with important improvements in respiratory mechanics during rest and exercise. This study also shows that traditional trough FEV<sub>1</sub> and oscillometry measurements appear to be adequately responsive to pharmacological interventions in mild COPD.

## Sources of support

Collaborative Innovative Research Fund, GlaxoSmithKline Canada. JG was supported by postdoctoral fellowships from the Natural Sciences and Engineering Research Council of Canada, the Canadian Thoracic Society and the Canadian Lung Association, and a New Investigator Award from the Providence Health Care Research Institute and St. Paul's Hospital Foundation.

## Conflicts of interest

JG and KW have no conflicts of interest to report. DO has received research funding from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck, Novartis, Nycomed and Pfizer; and has served on speakers bureaus, consultation panels and advisory boards for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Nycomed and Pfizer.

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